

# Neuroprotection: a new treatment modality for glaucoma?

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It is now commonly accepted that glaucoma is a neurodegenerative disease of the optic nerve. Thus, at any given time, there are neurons that, though still viable, are vulnerable to the hostile extracellular milieu and are therefore amenable to neuroprotective therapy. *Neuroprotection* refers to any intervention, either external to the optic nerve or internally, that will lead to an intracellular change in the balance between survival and death signals in favor of survival. Several potential sites and modalities for such intervention may exist. When designing neuroprotective therapy, ways must be sought to recruit the physiologic self-repair mechanisms awakened by the primary or secondary risk factors. These mechanisms appear to be insufficiently effective when in their natural state, but they may be simulated or boosted by appropriate therapeutic compounds or cells. *Curr Opin Ophthalmol* 2000; 11:107-111 © 2000 Lippincott Williams & Wilkins, Inc.

The concept of neuroprotection as a therapeutic strategy for glaucoma is not entirely new (even classic antihypertensive treatment may be viewed as neuroprotective) except in the sense that it shifts the focus of therapeutic endeavor from external risk factors (*i.e.*, extracellular environmental factors imposed on the nerve) to internal factors (*i.e.*, factors derived from the nerve itself). Traditionally, glaucoma has been regarded as a disease caused by changes such as increased intraocular pressure (IOP) in the extracellular environment of the optic nerve. Studies have therefore been aimed at identifying the environmental factors that cause the optic neuropathy. The current view is that glaucoma is a neurodegenerative disease that is triggered by an external factor or factors, in which ongoing degeneration is propagated not only by factors external to the nerve (risk factors) but also by factors derived from the nerve itself [1].

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## Abbreviations

CNS	central nervous system
IOP	intraocular pressure

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## Glaucoma as a neurodegenerative disease amenable to neuroprotective therapy

A number of insights may be considered as landmarks in shaping the current view of glaucoma as a disease that is neurodegenerative in character and therefore amenable to neuroprotective therapy. First, increased IOP has long been considered to be the most important risk factor in glaucoma, and reduction of IOP has therefore been the treatment of choice in attempting to arrest or at least retard the propagation of optic neuropathy and the loss of retinal ganglion cells in patients with glaucoma [2]. However, many patients with glaucoma continue to experience visual field loss long after therapeutic normalization of their IOP [3]. In addition, as many as one sixth of all patients with glaucomatous damage show no evidence of elevated IOP, even on repeated testing [4]. These findings suggest that, at least in some cases, high IOP alone cannot explain the propagation of glaucomatous optic neuropathy and that additional primary risk factors are involved.

Second, it is recognized that as the disease progresses, the nerve itself contributes to the hostile conditions and hence to the pathogenesis of the disease. For example, abnormally high levels of glutamate and nitric oxide, both known to be associated with neuronal degeneration, have been demonstrated in patients with glaucoma [5,6]. This implies that therapeutic intervention need not be restricted, as in the past, to neutralization of the primary risk factors. Third, it is recognized that ongoing changes

in the extra- and intracellular milieu of the nerve can cause molecular changes in the neurons that might affect their resistance [7] or susceptibility [8] to the induced hostility. Therefore, for example, in this hostile environment, neurons that are still viable might succumb to even a slight increase in glutamate toxicity.

Fourth, it is recognized that the molecular and cellular mechanisms that operate in other degenerative diseases may also be applicable to glaucoma [9]. Finally, it is recognized that the death of retinal ganglion cells in glaucoma is a gradual process, involving intracellular changes that may be amenable to intervention [10].

### **Progress in glaucoma therapy**

In the past, the therapeutic approach to glaucoma was targeted at external risk factors. Once glaucoma came to be viewed as a neurodegenerative disease, however, it became possible to consider neuroprotection as a potential therapeutic strategy [11]. Among the possibilities for neuroprotective treatment are the elimination of risk factors (in which case IOP reduction, the classic treatment for glaucoma, should also be viewed as a form of neuroprotection); neutralizing the toxicity of risk factors (*eg*, by using glutamate receptor antagonists [12,13] or inhibitors of nitric oxide synthase [14–20]); and increasing neuronal resistance to the external or internal risk factors [15].

The extent of neuronal degeneration following pathogenic or traumatic injury to the central nervous system (CNS) is a reflection of the direct (primary) damage to neurons or the withholding of target-derived trophic support from the cell bodies as a result of the primary insult. It is also a reflection of the subsequent (secondary) degeneration of neighboring neurons that escaped the initial injury but succumb to the toxic environment created in the vicinity of the degenerating nerve fibers and their cell bodies. Several mediators of toxicity have been identified, among them glutamate, free radicals, and high K<sup>+</sup> levels [16,17]. If optic nerve neuropathy is viewed as degeneration of the optic nerve, it seems reasonable to assume that such mediators of toxicity might be operating in glaucoma. Confirmation of this assumption comes from studies showing that glutamate is present in higher than physiologic amounts in the eyes of patients with glaucoma [5]. Therefore, the increased levels of glutamate may be viewed as a secondary risk factor, which could explain the exacerbation of glaucomatous damage initiated by the increased IOP. Another physiologic compound that might contribute to disease progression as a result of its abnormally high content in the injured CNS is nitric oxide [6].

It therefore seems that physiologic compounds whose normal levels are exceeded in response to the damage caused by a primary risk factor (such as IOP) in glaucoma may contribute to the progression of degeneration, even

after the primary risk factor itself has been alleviated or removed. If self-emitting physiologic compounds (such as glutamate or nitric oxide) at above-normal levels are responsible for the progression of neuronal degeneration, ways should be found to neutralize them, compete with them, or increase the resistance of the vulnerable neurons to them. This promising neuroprotective approach is now being tested experimentally as a therapeutic strategy in cases of CNS trauma [18,19] and neurodegenerative diseases [20]. The applicability to glaucoma has been suggested [1,11] and is currently a major research focus in glaucoma [15,21–22,23,24].

As mentioned previously, the environmental deficiency or toxicity created by the degenerating nerve causes further neuronal damage. It seems, however, that the primary and secondary causative factors, whether external (toxicity) or internal (deprivation of target-derived trophic support), not only trigger destructive processes but also awaken mechanisms of self-repair [7,25]. In the case of glaucoma, however, it seems that these self-repair mechanisms are either too weak or too short-lived to override the harmful effects.

In this connection, it is interesting to note that for glutamate, which exhibits essential physiologic activity or lethal neurotoxicity depending on its concentration, there is an intermediate level at which it not only is not detrimental but is even beneficial in triggering an intracellular mechanism of self-protection. We found that native neurons exposed to above-normal—though subtoxic—levels of glutamate develop a transiently increased resistance to further toxicity, and not necessarily to glutamate toxicity only [26]. The fact that the resistance induced by such glutamate levels is short-lived and is not restricted to glutamate toxicity has a number of implications: First, a ubiquitous amino acid, which is potentially neurotoxic, might be safe at a certain intermediate level. Second, a mechanism of self-repair might operate constitutively after insults to the nerve; and, finally, by gaining an understanding of a physiologically beneficial mechanism of repair, such as that mediated by glutamate, it might be possible to simulate it by appropriate drug therapy.

Another possible mechanism of intracellular self-repair is the induction of immediate early genes (such as c-JUN), which are found to be triggered immediately after optic nerve injury [27], apparently as a result of trophic factor deprivation. The increase is transient and can be sustained by a peripheral nerve graft, known to increase the survival rate and promote regrowth of injured optic nerve axons. A transient increase in brain-derived neurotrophic factor was also found to occur soon after optic nerve mechanical insult or as an early response to exposure to N-methyl-D-aspartate [28].

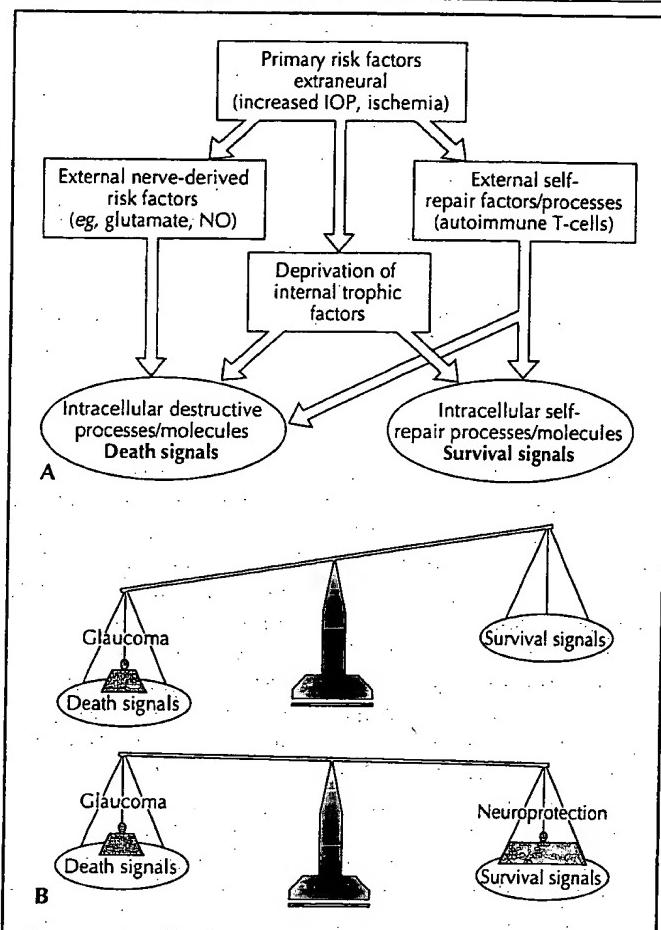
In the course of our studies of the mechanically crush injured optic nerve of adult rats [29<sup>a</sup>], we recently came across another mechanism, traditionally viewed as detrimental, which may be similar in nature to the physiologic self-repair mechanisms described here. The self-repair mechanism in this case operates externally to the optic nerve and is mediated by autoimmune T cells directed against a CNS antigen. In its normal state, this mechanism appears to be too weak to be effective, yet it is amenable to exogenous boosting and potentially lethal to the tissue if it gets out of control. We suggested that the endogenous T-cell immune response to optic nerve damage is beneficial but limited. Our findings showed, against all expectations, that exogenous administration of T cells directed against the CNS self-antigen myelin basic protein significantly reduces the injury-induced spread of degeneration [30<sup>a</sup>,31<sup>a</sup>]. This boosting of the neuroprotective autoimmunity was achieved, without accompanying autoimmune disease, by the adoptive transfer of T cells with selective activity to nonencephalitic self-epitopes [30<sup>a</sup>]. It is conceivable that the endogenous T cells that accumulate spontaneously at sites of CNS injury arise from an injury-triggered autoimmune response [32]. It might therefore be worth seeking ways to augment therapeutically a beneficial autoimmune response without triggering a persisting autoimmune disease. Such boosting might be achieved, *e.g.*, by employing T cells specific to the self-antigenic epitopes normally sequestered in the intact CNS. These autoimmune T cells would not accumulate in or interact with undamaged sites, and therefore would not induce disease, yet they might be able to assist in the repair of injured CNS tissue if the covert epitope is exposed by the injury.

T cells can synthesize cytokines and neurotrophic factors [33,34]. We have suggested that the accumulated autoimmune T cells may exert their neuroprotective effect by providing a source of neurotrophic factors. If so, these could compensate for the deprivation in supply or local production of trophic factors after injury to the optic nerve. Such an effect would illustrate the advantage of immune neuroprotection mediated by cells, rather than by pharmaceutical or physiologic compounds. The immune neuroprotection may represent an extracellular mechanism of self-repair.

### Testing the applicability of neuroprotective therapy to glaucoma

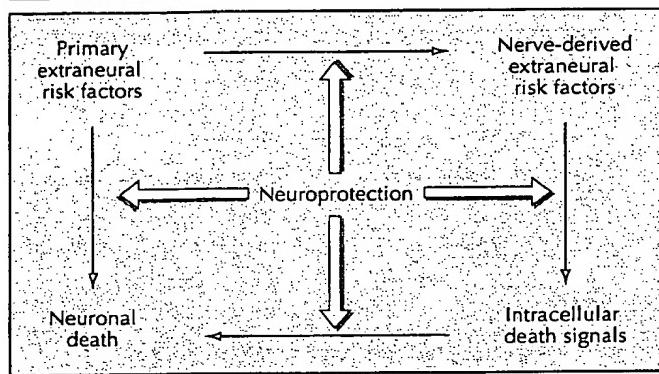
The antihypertensive drugs used for IOP reduction do not necessarily have any effect on the damage caused by nerve-derived risk factors. In this regard, neuroprotection is an untested strategy in glaucoma. Testing of a treatment modality for any disease may be hampered by the lack of availability of a suitable animal model. For example, we may be able to simulate in an animal the clinical manifestations of a particular disease, while lacking the ability to simulate the etiology.

**Figure 1. Factors affecting the intracellular balance between survival and death signals**



**A. Self-destructive and self-repair processes caused by risk factors external to the nerve.** External risk factors trigger processes that give rise to beneficial or detrimental changes in both the external and the internal environment of the nerve. **B.** These changes lead to further intraneuronal changes, which may be either beneficial (tending to self-repair) or detrimental (leading to death). The balance between the survival signals and the destructive signals leads, in most cases, to cell death. Any neuroprotective intervention may shift the balance toward neuronal survival.

As discussed previously, glaucoma has traditionally been thought of as a disease associated with increased IOP. Accordingly, animals with an experimentally induced increase in IOP have been used as models [35<sup>a</sup>], as their ocular characteristics are similar to those of patients with glaucoma. In such models, as in patients with glaucoma, well-known mediators of toxicity (such as glutamate and free oxygen radicals in high concentrations) have been detected [5,36]. The question then arises: What is the most appropriate model for testing neuroprotective strategies aimed at neutralizing the effects of a toxic environment? The model of choice for this purpose is one that will show self-perpetuating degeneration after a primary external insult, and one in which mediators of toxicity can be detected.

**Figure 2. Potential sites of neuroprotective intervention**

We have developed a model of a partial crush injury of the rat optic nerve in which neurons that escaped the primary crush injury continue to degenerate even in the absence of any external insult [29<sup>o</sup>], and toxic compounds such as glutamate and aspartate are detectable [37]. Using this model, we were able to demonstrate the neuroprotective activity of compounds that act directly on the neurons by competing with the mediators of toxicity for binding to their receptors (*eg*, *N*-methyl-D-aspartate antagonists) [13], or indirectly by modifying the extracellular milieu, leading to intracellular changes in death and survival signals and therefore altering the resistance of neurons to the toxicity [38]. The findings in our model, as well as the results of neuroprotection studies using other animal models of injured optic nerves, all point to the conclusion that neuroprotective compounds shown to be effective against CNS trauma outside the visual system are also active in the optic nerve, regardless of the nature of the primary insult.

### Drugs in neuroprotective therapy

It may not be necessary to add a new compound to the drug treatment used in glaucoma, as some of the drugs used to reduce pressure may also under certain conditions be neuroprotective against environmental hostility. It is worth mentioning that an  $\alpha$ -2 adrenoreceptor agonist with antihypertensive properties was recently shown to be neuroprotective after crush injury (unrelated to pressure) in the rat optic nerve model [39<sup>o</sup>]. The effect of the drug was receptor mediated and was indirect; *ie*, it resulted in the production of a supportive extracellular milieu, which in turn produced intracellular conditions favoring cell survival [40].

In this context it is worth mentioning glutamate, a known physiologic compound that, surprisingly, displays a neuroprotective effect. Glutamate, which normally acts as a major neurotransmitter but is highly neurotoxic at high concentrations, can at certain intermediate levels be neuroprotective [26<sup>o</sup>]. Although we are not suggesting

that glutamate is potentially a neuroprotective compound, an understanding of the self-protection molecular mechanisms awakened by glutamate may lead to the development of drugs that will mimic this beneficial biologic effect, without the toxic side effects. This unexpected property of glutamate suggests that this amino acid might represent a family of physiologic compounds that possesses both benign biologic activity and cytotoxicity and that can operate at a level of safety where the system is not only not in danger from but is actually protected from toxicity.

### Conclusions

Glaucoma may be viewed as a neurodegenerative disease. The death of cell bodies of the directly damaged nerve fibers (induced by risk factors external to the nerve) occurs at a relatively late stage of the degenerative process, therefore leaving a window for therapeutic intervention. In addition, the progressive death of retinal ganglion cells, even when the external factors are kept under control, may be a reflection of both internal and external factors derived from the nerve itself (Fig. 1a). These emerging factors trigger intracellular signals for both death and survival, and the balance between these signals will determine the fate of any neurons that are still viable within the hostile environment of the nerve (Fig. 1b). Neuroprotection may operate on several levels, including elimination of detrimental factors external to the nerve, blocking of nerve-derived self-destructive factors, and influencing the intracellular signaling balance in favor of survival (Fig. 2).

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# The mechanism of action of prostaglandins on uveoscleral outflow

Undine Schachtschabel, PhD, James D. Lindsey, PhD, and Robert N. Weinreb, MD

It is generally accepted that prostaglandins (PGs) lower intraocular pressure by increasing uveoscleral outflow. The growing use of PGs to lower intraocular pressure has led to increased interest in the uveoscleral outflow. Uveoscleral outflow passes through extracellular spaces within the ciliary muscle and then through the suprachoroidal space to the posterior pole of the eye. Recent studies indicate that this reflects a direct effect of PGs on specific ciliary muscle prostanoid receptors. Activation of these receptors stimulates several linked responses, including cAMP formation and induction of c-Fos and c-Jun expression. These signals lead to increased biosynthesis of matrix metalloproteinases, a family of neutral proteinases that can cleave extracellular matrix molecules. These matrix metalloproteinases may initiate the alteration of collagens in the ciliary muscle to increase spaces among ciliary muscle fibers, thereby reducing hydraulic resistance in the uveoscleral outflow pathway. *Curr Opin Ophthalmol* 2000; 11:112–115 © 2000 Lippincott Williams & Wilkins, Inc.

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## Abbreviations

ECM	extracellular matrix
MMP	matrix metalloproteinase
PG	prostaglandin
TIMP	tissue inhibitors of matrix metalloproteinases

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The mechanisms underlying the pressure-lowering effect of topically applied prostaglandins (PGs) are not completely understood. However, experimental studies identified several cellular responses and features that appear to work together. First, the ciliary muscle contains several different PG receptors, mainly FP and EP<sub>2</sub> receptors [1,2]. These PG receptors can activate adenylyl cyclase and phospholipases via distinct G-proteins, with the subsequent generation of the second messengers inositol 1,4,5-triphosphate (IP<sub>3</sub>) and cyclic AMP. Recent experiments in cultured human ciliary muscle cells have confirmed that an increase of intracellular cAMP occurs after exposure to PGF<sub>2α</sub> [3]. This leads to an activation of nuclear regulatory proteins, including c-Fos and c-Jun [4,5], followed by increased biosynthesis of matrix metalloproteinases (MMPs), a family of secreted proteases that can cleave collagens and other extracellular structural proteins [6,7]. In addition, there is reduction in the ciliary muscle content of the extracellular matrix molecules collagen type I, collagen type III, and collagen type IV [8,9•]. These responses paint a plausible scenario for a PG-mediated opening of the uveoscleral pathway in the ciliary muscle by reducing extracellular matrix in the spaces among ciliary muscle fibers. Therefore, induction of MMPs, and the coordinated regulation of their natural inhibitors, called tissue inhibitors of matrix metalloproteinases (TIMPs) [10], may contribute to the ocular response to topical PGs. Also, an imbalance of MMP and TIMP expression might represent an important factor in the pathophysiology of primary open-angle glaucoma.

## Clinical relevance

The clinical usefulness of PG-based drugs has been enhanced by chemical modifications of the parent natural PG that improve specificity for certain receptors and improve corneal penetration through increased lipophilicity. Several of those PGF<sub>2α</sub>-substitutes have shown improved therapeutic indices, *i.e.*, intraocular pressure reduction of about 4–8 mmHg with minimal side effects. These include PGF<sub>2α</sub>-IE (isopropylester), isopropyl unoprostone, PhXA34 (17-phenyl substitute of PGF<sub>2α</sub>-IE), and PhXA41 (latanoprost, the more active R-epimer of PhXA34) [11]. Latanoprost has been used in clinical studies and multicenter clinical trials for the treatment of primary open-angle glaucoma [12–16]. It also has been used as adjunctive therapy [17–19], in combination with the β-adrenergic receptor blocker timolol [20,21], adrenergic agonists (dipivefrin) [22], or the carbonic anhydrase